REMARKS

All previous rejections were overcome and a new set of rejections were issued. This paper responds to the new rejections.

A single new claim has been added, claim 36. It is a dependent claim which recites a gene that was observed to be most differentially expressed in the examples. See Table 1.

Objection to the specification

The specification was objected to because the numbering of the figures in The Brief Description Of The Drawings did not match the drawings. The specification has been corrected to correspond to the drawings.

Rejection of Claims 1-18 under 35 U.S.C. §112, 1st Paragraph

Claims 1-18 stand rejected for the alleged addition of new matter. This rejection is respectfully traversed.

Claim 1 originally recited a "first population" and a "second population." On October 11, 2007, applicants amended claim 1 to recite a "first human population" and a "second human population." Thus the newly added term was "human."

The U.S. Patent and Trademark Office states that the precise term "human population" was not used in the specification. Only "human individuals" and a subset of human individuals were allegedly used in the disclosed analysis.

Since the term "population" was used in the original claims, and the original claims form part of the disclosure, the term population itself cannot add new matter. The

U.S. Patent and Trademark Office acknowledges that human individuals and subsets of human individuals were disclosed in the specification. Thus it must also be true that human populations are disclosed. Subsets of human individuals constitute human populations. The distinction which the U.S. Patent and Trademark Office draws between the claimed subject matter (human population) and the disclosed subject matter (subsets of individuals) is not clear.

As the U.S. Patent and Trademark Office recognizes, human individuals and subsets are clearly disclosed throughout the whole application See for example paragraph 14 which discloses:

> Phenotypes which can be assessed according to the present invention are those which relate to disease as well as those which relate to normal human physiology. Examples of phenotypes include disease susceptibility, birth defects, psychological parameters, learning parameters, and physical characteristics. The phenotype is preferably a polymorphic phenotype, *i.e.,* many forms of the characteristic exist. Individuals who share a particular phenotype are grouped together and are termed "affected individuals" for purposes of this invention. Individuals who do not share the particular phenotype are used to form a control population.

Emphasis added. Thus the specification clearly discloses that humans are the subject of the disclosure and that groups of individuals form populations.

Paragraph 27 similarly makes clear that the disclosure relates to populations of humans:

> Second, expression data are independent of population structure and do not rely on the absence of recombination between the marker and the responsible gene. We anticipate that the approach described above or other methods for measuring allelic variation in gene expression will play a major role in defining normal human variation and disease susceptibility in the future.

It is respectfully submitted that human populations are indeed groups of individual humans. Groups of individual humans are disclosed in the specification. Thus the addition of the adjective "human" to modify "populations" in an original claim does not constitute new matter.

The MPEP § 2163 cites approvingly *Martin v. Johnson,* 454 F. 2d 746, 751, 172 U.S.P.Q. 391, 395 (C.C.P.A. 1972) as standing for the proposition that the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient" for the purposes of § 112, first paragraph. Even if, the precise term "human population" does not appear in the specification in *ipsis verbis,* the specification clearly discloses this subject matter. It does not, therefore constitute new matter.

The courts have described the essential question to be addressed in a written description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985)

(quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). The applicants have clearly conveyed in their specification that they had possession at the time of filing of the subject matter now claimed.

Withdrawal of this rejection is respectfully requested as no new matter has been added by the prior amendment.

Rejection of claims 1, 7, 9, 11-14, 16-18, 34, 35 under 35 U.S.C. §102 (b)

Claims 1, 7, 9, 11-14, 16-18, 34, 35 stand rejected under 35 U.S.C. §102 (b) over Egyed ("Analysis of Eight STR Loci in Two Hungarian Populations," Reference W). This rejection is respectfully traversed.

To reject a claim as anticipated, each and every element as set forth in the claim must be either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987). The current rejection fails because the cited reference does not describe each and every element as set forth in the claim.

The rejection urges that Egyed teaches a method comprising "determining levels of expression of an allele of a gene in a first human population….and in a second human population…" This interpretation of Egyed is incorrect. Egyed teaches the determination of DNA only. "DNA samples (0.5-2 ng) were coamplified using reagents provided in the AmpFISTR Profiler Plus PCR Amplification Kit. The PCR products were analyzed by fluorescence-based automated detection and capillary electrophoresis system on an ABI PRISM 310 Genetic Analyzer." Page 26, first full paragraph. This describes an assay of genes only. The amplified genes were sequenced to determine their sequence: "Sequencing was done with forward as well as reverse primers." Page 26,

second full paragraph. Egyed determined allele frequency values. Page 26, last paragraph. No determination of expression products or expression levels is disclosed.

The rejection points to Figure 1 as relevant. Figure 1 teaches the sequence structure and fragment length of four alleles. These are gene structures. These do not teach anything about gene expression, *i.e.,* the production of RNA and/or protein using the gene as a template.

Nothing in Egyed's disclosure teaches or suggests anything at all about expression of the genes, *i.e.,* the production of RNA and/or subsequent production of protein. The first ten definitions of gene expression found on the web are shown below:

- The process by which a gene's coded information is converted into the structures present and operating in the cell. ...
  www.genelabs.com/resources/glossary.html
- The process by which a genes coded information is converted into the structures present and operating in the cell. Expressed genes include those that are transcribed into mRNA and then translated into protein and those that are transcribed into RNA but not translated into protein.
  clanlindsay.com/genetic_dna_glossary.htm
- The process by which the information encoded in a gene is converted into protein or some form of RNA. The DNA sequence is first transcribed into RNA and then usually translated into protein.
  www.homepages.indiana.edu/120800/text/glossary.html
- The transcription of mRNA from the DNA sequence of a gene and the subsequent translation of that mRNA to give the protein gene product. Less strictly it can mean the transcription step alone. (10)
  www.plantpath.cornell.edu/glossary/Defs_G.htm
- The process by which a gene's information is converted into the structures and functions of a cell.
  usinfo.state.gov/journals/ites/1005/ijee/glossary.htm
- Not every gene is expressed in every cell. Expression refers to whether the protein coded by a gene is expressed or not.
  www.cgm.northwestern.edu/glossary.htm
- the full use of the information in a gene through transcription and translation leading to production of a protein.
  www.nutrabio.com/Definitions/definitions_g.htm
- The process by which genes are first converted to messenger RNA and then to proteins.
  publications.nigms.nih.gov/thenewgenetics/glossary.html
- The process by which genes express themselves: in the cell, gene expression results in the manufacture of proteins that determine an organism's characteristics.
  www.exploratorium.edu/genepool/glossary.html
- The actual production of the protein which the gene encodes.
  www.abc.net.au/science/slab/genome2001/glossary.htm

As can be seen from these definitions, genes alone and their frequency of occurrence does not constitute gene expression. Yet this is all that Egyed has taught.

The discussions of determining of levels of expression in the specification does not vary from the accepted meanings in the art:

> Levels of expression of an allele can be determined using any techniques which are known in the art. Such techniques include but are not limited to allele-specific expression assays, oligonucleotide ligase assays, and dideoxy single-base extension of an unlabeled oligonucleotide primer, described in more detail below. Any technique can be used that can distinguish between expression products of alleles. The level of expression of a single allele of a gene can be determined in isolation, without comparing expression to the second allele present in an individual. Alternatively, the level of expression of one allele of a gene in an individual can be compared to the level of a second allele of the gene in the individual.
>
> Levels of expression are compared to determine statistically significant differences. Any statistical analysis can be used which determines such differences. One particular analysis which can be used is the MIXED procedure of the SAS system version 8.0 for repeated measurements. A statistically significant difference can be a 5 % difference, a 10 % difference, a 15 % difference, a 20 % difference, a 25 % difference, or more.

Page 5, paragraphs 15 and 16, emphasis added.

Because Egyed teaches only gene frequencies, not levels or amounts of gene expression, Egyed does not teach each and every limitation of the claim. A reference that does not teach each and every limitation of the claim, explicitly and/or inherently, *cannot* anticipate claimed subject matter.

Please withdraw the rejection for failing to comply with the statutory requirements for anticipation.

Rejection of claims 1-2, 7, 11-13, 15-17 under 35 U.S.C. §102 (b)

Claims 1-2, 7, 11-13, 15-17 stand rejected under 35 U.S.C. §102 (b) over Sieber et al. ("Whole-gene APC deletions cause classical familial adenomatous polyposis, but not attenuated polyposis or "multiple" colorectal adenomas," Reference X). This rejection is respectfully traversed.

To reject a claim as anticipated, each and every element as set forth in the claim must be either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987).

Sieber teaches determining the structure of the APC exon 14 in various individuals. Sieber performs fine-mapping of the region and finds deletions. Deletions are a structural feature of DNA. Sieber studies only the structure of the genomic DNA. Seibel does not study the expression of the genomic DNA, *i.e.,* how it is converted into RNA or protein. Sieber teaches nothing at all about determining levels of expression of an allele of a gene.

Sieber discloses allele frequency in Table 2. This is the prevalence of an allele in a studied population. It teaches nothing at all about the level of expression, *i.e.,* in RNA or protein. Sieber characterizes the molecular genetic data that he generates as "gene dosage" and "genotype analysis." Page 2956, second column. These two types of data relate to the amount of copies of a gene (DNA) and a gene's constituent sequence or structure. Neither of these teach or suggest anything about expression levels.

Withdrawal of this rejection is appropriate because each of claims 1-2, 7, 11-13, 15-17 recites the determination of levels of expression of an allele of a gene and Sieber

fails to teach such a determination, explicitly or inherently. Because Sieber does not teach each and every step and/or element of the claims, Sieber cannot anticipate them.

Rejection of claims 1-4, 7, 10-13, 16, and 18 under 35 U.S.C. §102(b)

Claims 1-4, 7, 10-13, 16, and 18 stand rejected as anticipated by Griseri et al. ("A single-nucleotide polymorphic variant of the RET proto-oncogene is underrepresented in sporadic Hirschsprung disease"; Reference V). This rejection is respectfully traversed.

To reject a claim as anticipated, each and every element as set forth in the claim must be either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987).

Griseri et al, like Sieber and Egyed discussed above, does not anticipate the present invention because it does not teach anything at all about gene expression. Like the other references, Griseri studies gene structure, specifically a single-nucleotide polymorphic variant (a SNP) and the frequency of the structure in a population. See Table 1.

Griseri reports protein binding assays with the variant oligonucleotides to determine any differences in protein binding interactions due to the SNP. None were observed. See Figure 1. Griseri also reports the use of exon trapping experiments, but found that both alleles formed correctly spliced RNA. See Figure 2. Neither of these assays constitutes a determination of a level of expression. Since all of the rejected claims recite determining of expression levels and Griseri does not teach or suggest determining expression levels, Griseri cannot anticipate the presently rejected claim set.

Withdrawal of this rejection is respectfully requested.

Rejection of Claims 19-32 Under 35 U.S.C. §103(a)

Claims 19-32 are rejected as unpatentable over Griseri (Reference V) in view of Yoshikawa (Reference U). This rejection is respectfully traversed.

Claims 19-32, the only independent claims in the rejected claim set, are directed to methods for measuring allelic expression variation in a non-imprinted gene. Molecules of cDNA reverse transcribed and amplified from a heterozygous individual are hybridized to primers and the primers are differentially labeled dependent upon which of two alleles is present. The amount of the two primers is then compared.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka,* 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine,* 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). See M.P.E.P. § 2143.03.

Griseri is cited as teaching a method of detecting allelic expression. Office Action at page 9, line 16. The Office Action points to paragraph 3 on page 722 as teaching reverse transcribing mRNA from an individual and comparing the level of expression of an allele with a second allele. However, Griseri does not teach "comparing the level of expression of an allele with a second allele" as asserted. Griseri paragraph 3 of page 722 teaches only performing RT-PCR.

Yoshikawa is cited as teaching the differential labeling of primers. This teaching alone does not, however, remedy the deficiency of the primary reference, Griseri. Because Griseri does not teach comparing the level of expression of one allele to another within a single individual, as recited in claims 19 and 32, the rejection as a whole fails. Neither reference teaches this recited step or element of claims 19 and 32. Thus a *prima facie* case of obviousness has not been made.

Concluding Remarks

At itemized paragraph 8 of the Office Action on page 10, the U.S. Patent and Trademark Office finds a prior argument of the applicants unpersuasive because "the gene expression need not necessarily depend on mRNA and protein expression rather it is dependent on level of DNA expression." The meaning of this statement is obscure. Gene expression is a process which consists of RNA and/or protein synthesis. There is no separate and independent entity called "DNA expression." When DNA is made from a DNA template, the process is generally termed DNA replication. DNA replication is not a form of "expression." Expression, like DNA replication, uses a DNA template, but it makes RNA. The term expression also encompasses the subsequent step where RNA is translated into protein.

Thus the term gene expression refers to the biological process that uses a gene (DNA) as a template for the synthesis of RNA. It further refers to the process of translating the RNA so synthesized into protein.

The U.S. Patent and Trademark Office points to page 5 of the specification as teaching various DNA techniques to determine level of gene expression. These techniques, to the extent that they are DNA techniques, require a prior step of reverse

transcription to be used. Thus mRNA is first reverse transcribed to DNA, and then the DNA analytic technique can be used to *indirectly* analyze the mRNA, *i.e.,* a product of gene expression. Thus structural or even quantitative analysis of genomic DNA does not determine or measure levels of expression.

Withdrawal of the current rejections and a speedy allowance of all claims are respectfully requested.

Respectfully submitted,

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By: /Sarah A. Kagan /
Sarah A. Kagan
Registration No. 32,141

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